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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/743,625 | 12/22/2003 | Arthur M. Krieg | C1039.70073US00 | 9416 |

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Helen C. Lockhart, Ph.D.
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

| EXAMINER | |
|---|---|
| MINNIFIELD, NITA M | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/743,625 | KRIEG ET AL. | |
| | Examiner | Art Unit | |
| | N. M. Minnifield | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *19-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicants' amendment filed December 17, 2007 is acknowledged and has been entered. Claims 1-18 have been canceled. Claims 19-39 are now pending in the present application. All rejections have been withdrawn in view of Applicants' comments with the exception of those discussed below.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an

invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42-47, 49-53, 56, 57, 82-85, 90, 92, 94, 96, 98, 100, 102 and 103 of copending Application No. 09/337584. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method for treating asthma in a subject, comprising administering to the subject an effective amount for treating asthma in the subject of an immunostimulatory oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46, 52, 64, 71, 72, 74 and 80 of copending Application No. 10/613739. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method comprising administering to the subject an immunostimulatory oligonucleotide. Although 10/613739 does not recite treatment for asthma, this would be the result since the methods steps are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 23, 31, 32 and 34-37 of copending Application No. 10/769282. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method comprising administering to the subject an immunostimulatory oligonucleotide. Although 10/769282 does not recite treatment for asthma, this would be the result since the methods steps are the same. Application 10/769282 recites a method of modulating an immune response, the administration of the immunostimulatory oligonucleotide modulates a Th1 immune response, which is the immune response modulated in an asthmatic subject that has received the immunostimulatory oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6 Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-29 and 31-33 of copending Application No. 10/894862. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method comprising administering to the subject an immunostimulatory oligonucleotide. Although 10/894862 does not recite treatment for asthma, this would be the result since the methods steps are the same. Application 10/894862 recites a method of inducing a Th1 immune

response and suppressing a Th2 immune response, the administration of the immunostimulatory oligonucleotide modulates a Th1 immune response, which is the immune response modulated in an asthmatic subject that has received the immunostimulatory oligonucleotide; the Th2 immune response is suppressed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. The provisional obviousness-type double patenting rejection over 09/337584, 10/613739, 10/769282 and 10/894862 is maintained. Applicants' arguments filed December 17, 2007 have been fully considered but they are not persuasive. Applicants have asserted that the rejections are provisional since none of the claims in the 09/337584, 10/613739, 10/769282 and 10/894862 applications have been found allowable. If any of the cited claims are found allowable, Applicants will address the rejection. With regard to 09/337584, Applicants have indicated that they will consider filing a terminal disclaimer if the claims are allowed after the Interference. With regard to 10/613739, Applicants have asserted that this application is not commonly owned over the instant claims; however it is noted that there is a common inventor, Krieg. With regard to 10/769282 and 10/894862, it is requested that the rejection be held until allowable subject matter in any of the cited applications is identified. The provisional rejection will be maintained until a properly filed terminal disclaimer is received.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 19-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The pending claims (claim 19, for example) are directed to a method of treating asthma comprising: administering to a subject an immunostimulatory oligonucleotide comprising an immunostimulatory motif comprising a 5'-cytosine-guanin-3', wherein the immunostimulatory oligonucleotide is administered without an allergen in an amount effective to treat asthma.

The claims do not recite that the immunostimulatory motif comprising a 5'-cytosine-guanin-3' is unmethylated.

The state of the art teaches that the unmethylated CpG in these immunostimulatory oligonucleotides are responsible for the immune stimulatory activity in view of the fact that when these motifs are methylated the activity is lost (Krieg, Trends in Microbiology, June 2001, 9/8:249-252; see also Verthelyi et al, Clinical Immunology, 2003, 109:64-71). Lin et al (J. Invest. Medicine, September 1997, 45/7:333A abstract only) teaches that oligodeoxynucleotides containing unmethylated CpG dinucleotides are capable of inducing activation of cells including B cell and monocytes/macrophages that participate in antigen presentation.

The claims 19, 20 and 28-39 do not define the structure of the immunostimulatory oligonucleotide comprising an immunostimulatory motif comprising a 5'-cytosine-guanine-3'. What is the exact structure of the immunostimulatory oligonucleotide? The claims only recite that it must contain a

5'-cytosine-guanine-3'. The structure is not defined. The state of the art is unpredictable with regard to the use of oligonucleotides of less than 8 nucleotides having immunostimulatory activity.

Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that "immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long." (abstract). The state of the art with regard to the CpG oligonucleotides and stimulating a Th-1 immune response (treating an allergic response to an antigen or allergy related disorder during antigen specific immunotherapy of a subject) is unpredictable. The state of the art teaches that there are a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule. For instance, Krieg (BioDrugs 1998, 5:341-346) teaches that synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by s-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity (p. 342). Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that "immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less

in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long." (abstract). Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (p. 119). Further, Agrawal et al. teach that "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity..." (See p. 1 14, bottom of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is 'GTCGTT or TTCGTT" (p. 115). Thus indicating that an oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans. Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility,. ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the non-bridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (see p. 1618). Therefore, in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from

nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage. Further, Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) teaches that although "ISS are generally considered by researchers in this field to be modular 6-mer units, it has been difficult to determine the minimum stimulatory motif length. One study showed that a minimum length of 18 bases was required but that a length of 22 bases gave greater activity. Another study demonstrated good activity with a 15-mer ODN. Still another study used cationic lipid transfection to show a stimulatory effect with a 6-mer ODN." (p. 904, col. 1) Van Uden et al teaches that each ISS appears to have a different minimum length because crucial flanking bases would be variably distant from the core (p. 904, col. 2).

In view of all of the above it would require undue experimentation to practice the claimed invention. Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to a method of treating asthma comprising: administering to a subject an immunostimulatory oligonucleotide comprising an immunostimulatory motif comprising a 5'-cytosine-

guanin-3', wherein the immunostimulatory oligonucleotide is administered without an allergen in an amount effective to treat asthma, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the nature of the invention and (5) the state of the prior art, these have been discussed above. One of skill in the art would require guidance, in order to make or use the method and immunostimulatory nucleic acids as claimed. For reasons stated above (i.e. lack of enabling disclosure, unpredictability of the art, and lack of guidance) it would require undue experimentation to practice the claimed invention. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In view of all of the above, the pending specification does not enable the claimed invention and therefore the pending claims are not enabled.

10. No claims are allowed.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

N. M. Minnifield
Primary Examiner
Art Unit 1645

/N. M. Minnifield/
Primary Examiner, Art Unit 1645
April 13, 2009